

Figure 1

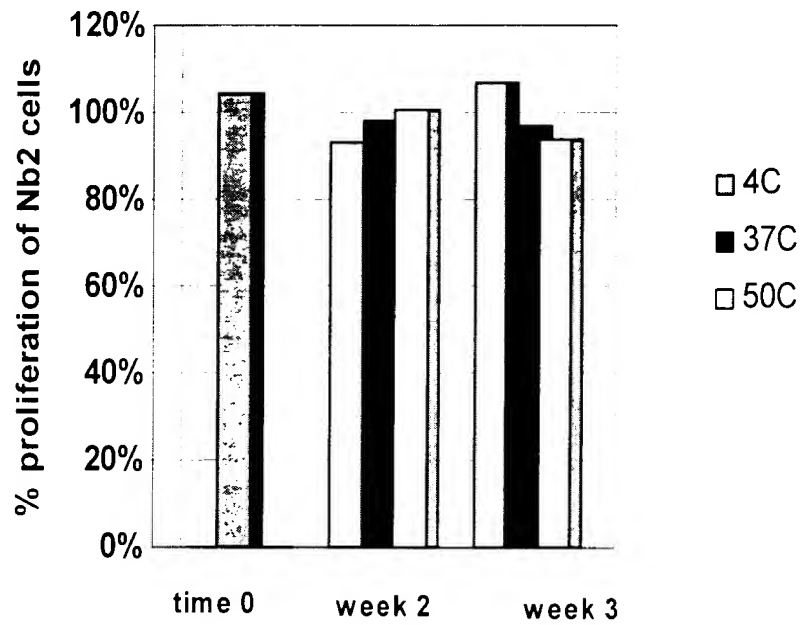


Figure 2

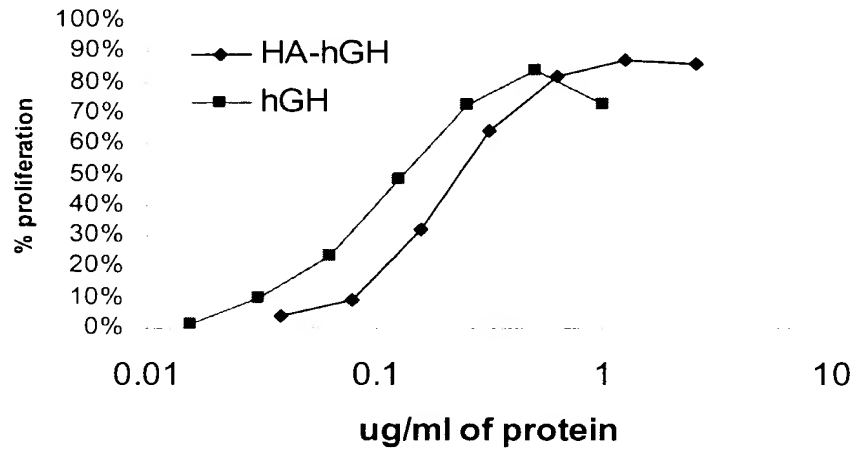


Figure 3A

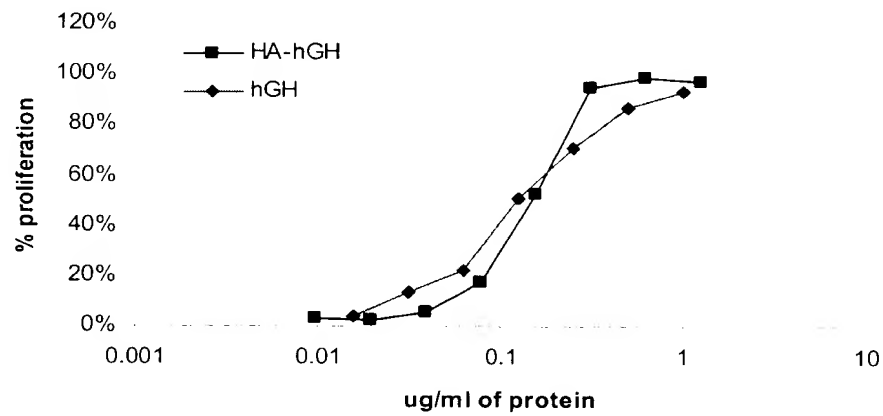


Figure 3B

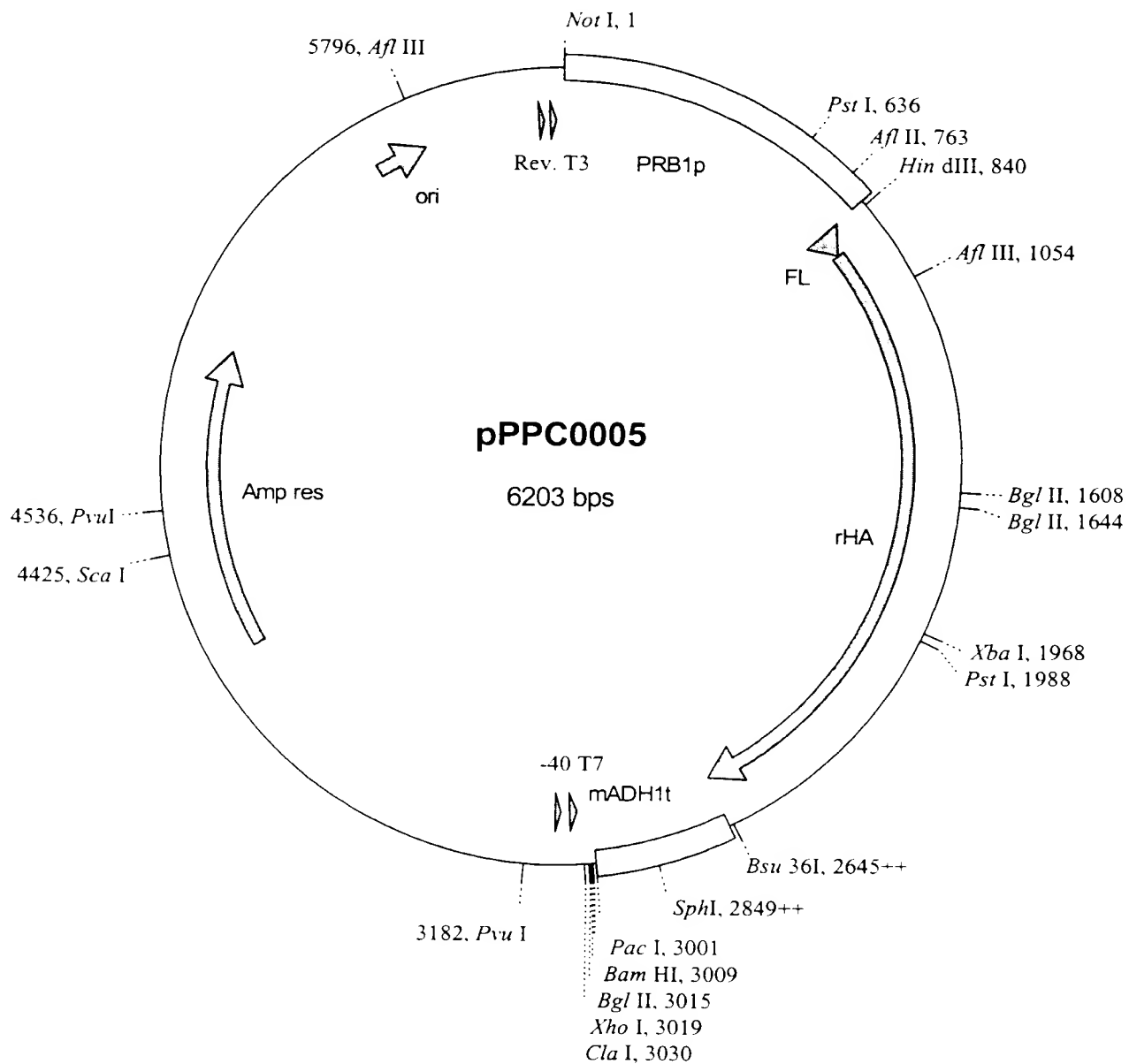


Figure 4

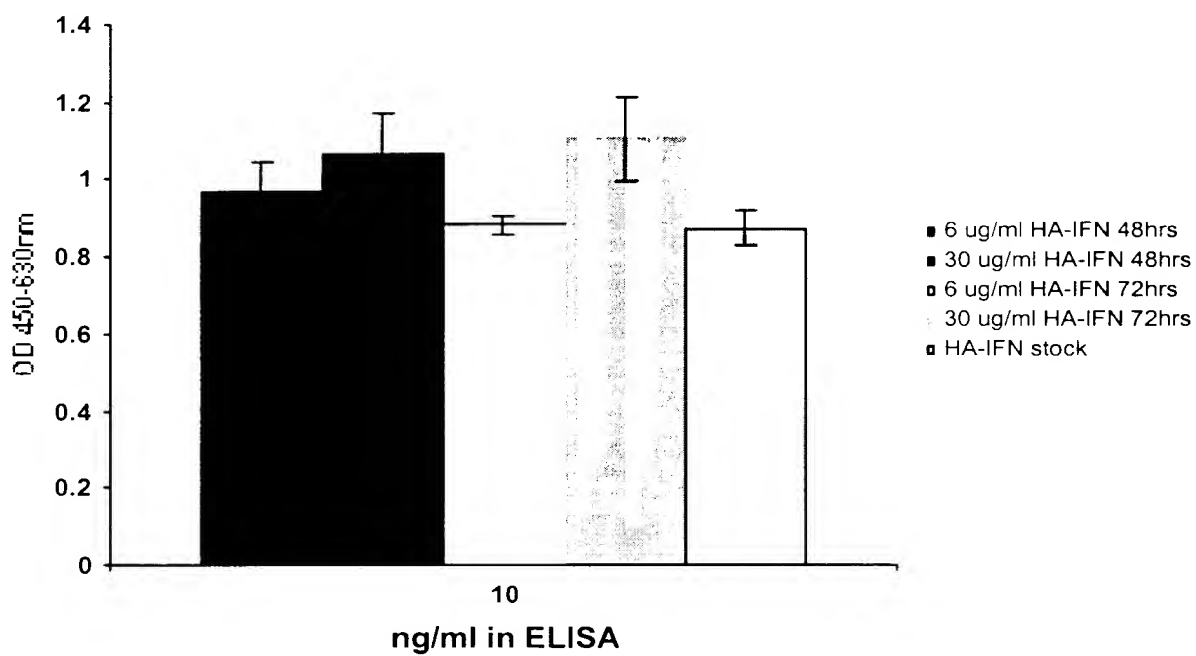


Figure 5

Figure 6

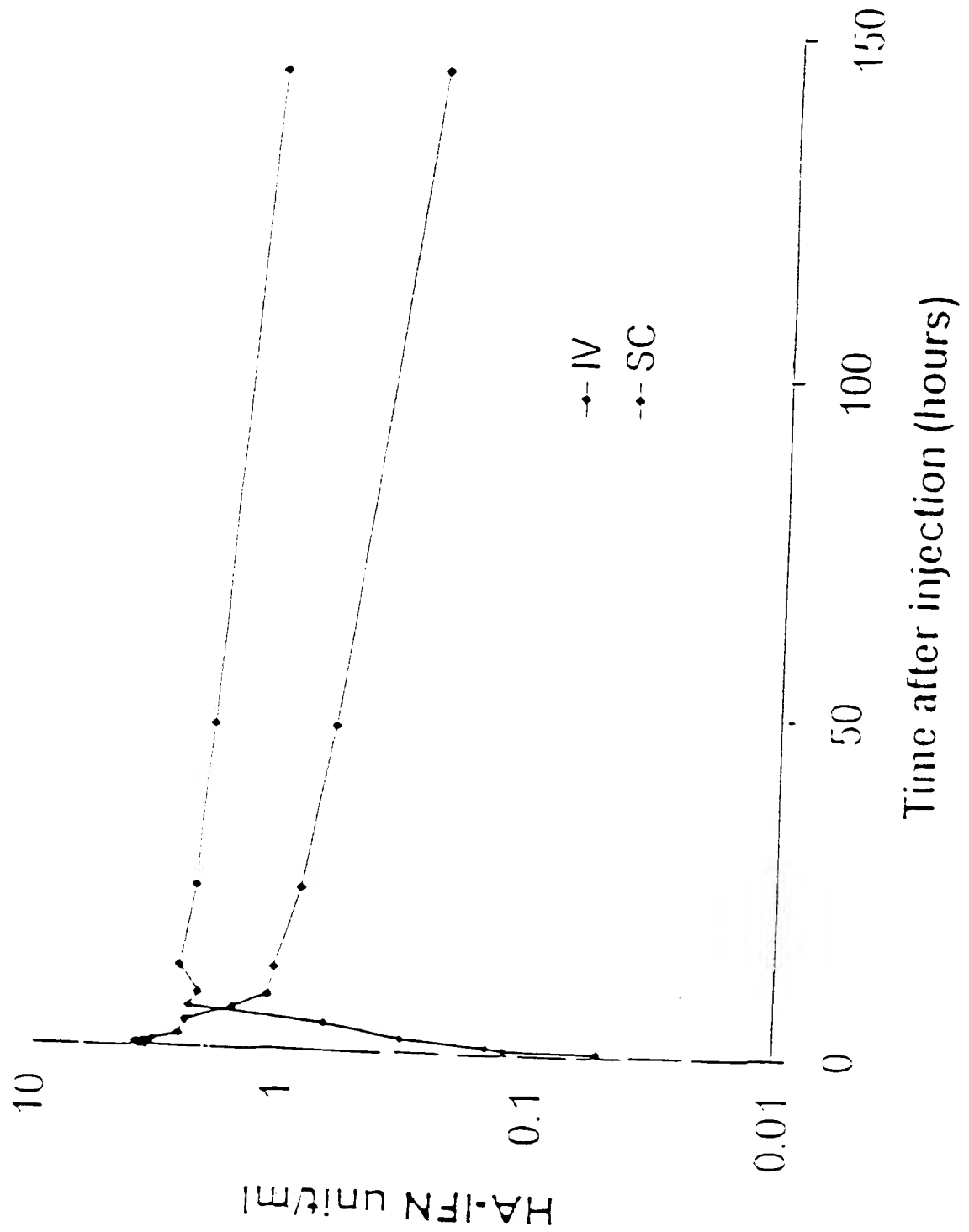
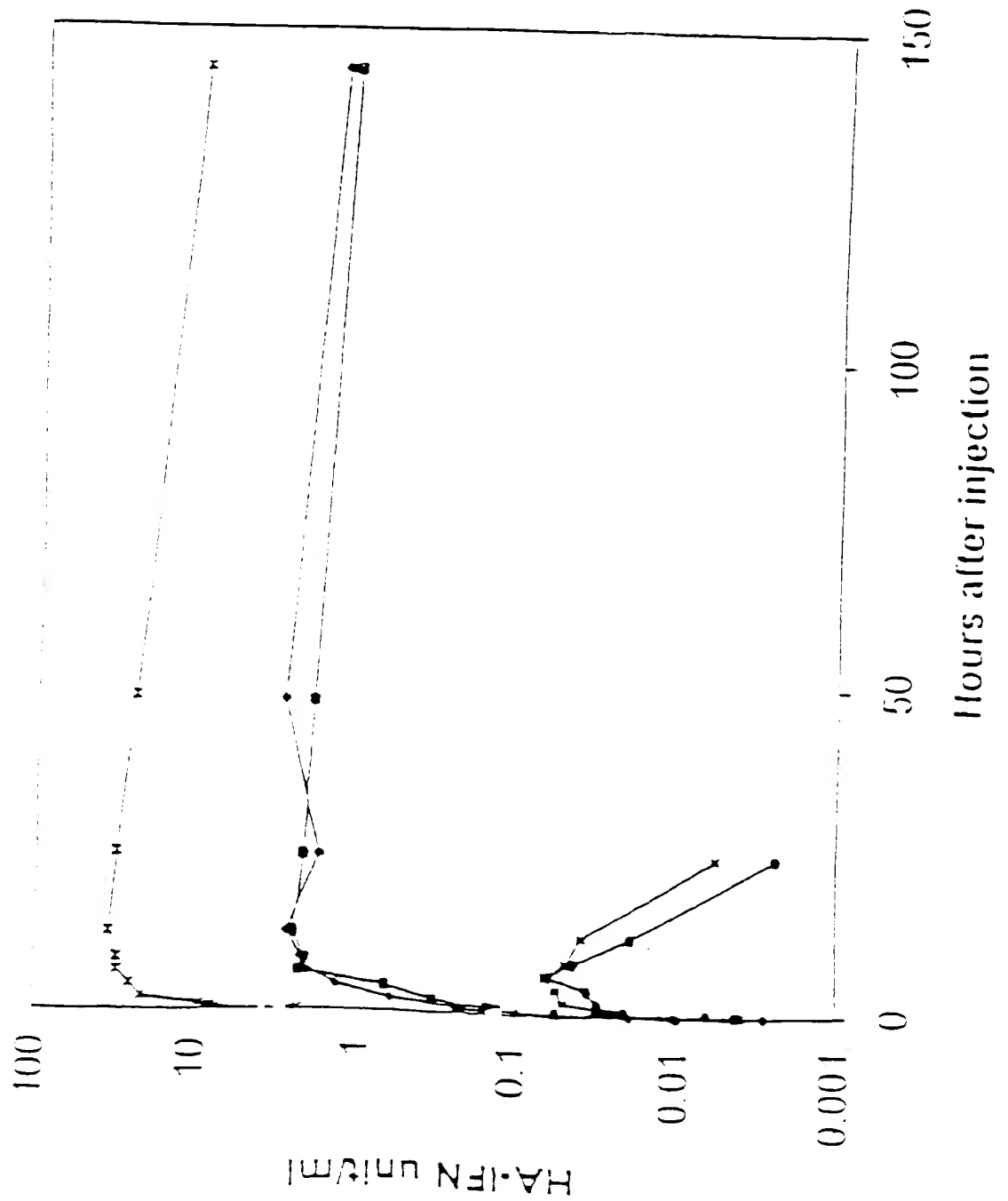


Figure 7



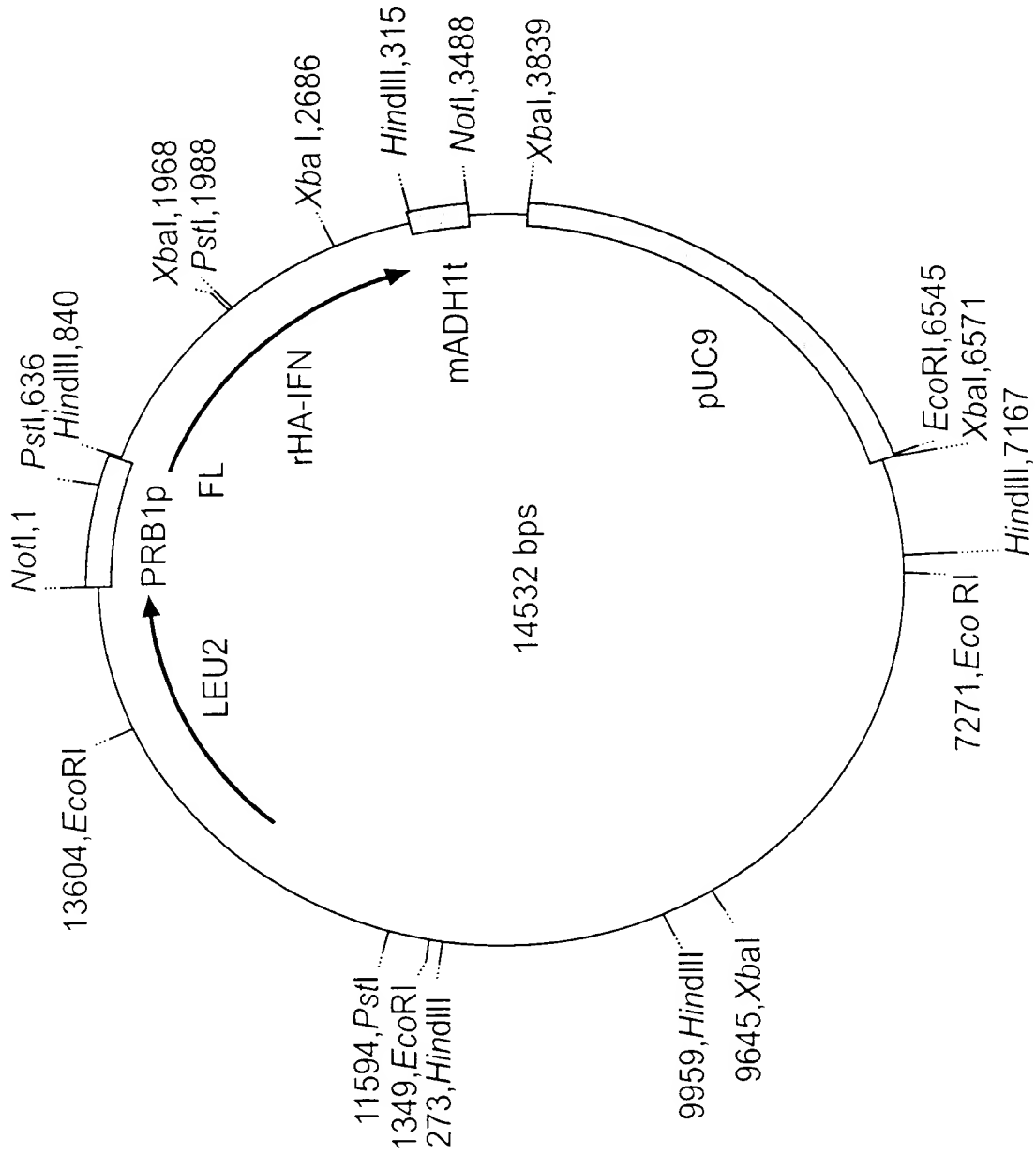


FIG. 8

Figure 9

```

1   DAHKSEVAHR FKDLGEENFK ALVLIAFAQY LQQCPFEDHV KLVNEVTEFA
      HHHHH HHH      HHH HHHHHHHHHHH      HHHHH HHHHHHHHHHH

      I                      II                      III
51  KTCVADESAE NCDKSLHTLF GDKLCTVATL RETYGEMADC CAKOEPERNE
      HHHHH      HHHHH HHHHH      HHHH H      HHHH

101 CFLQHKDDNP NLPRLVRPEV DVMCTAFHDN EETFLKKYLY EIARRHPYFY
      HHHH      H      HHHHHHHHH      HHHHHHHHH HHHHH

      IV
151 APELLFFAKR YKAAFTECCO AADKAACLLP KLDELRLDEGK ASSAKQRLKC
      HHHHHHHHHHH HHHHHHHHH      HHHHH HHHHHHHHHHH HHHHHHHHHHH

      V
201 ASLQKFGERA FKAWAVARLS QRFPKAEFAE VSKLVTDLTK VHTECCHGDL
      HHHHH      HH HHHHHHHHHHH HH      HHH HHHHHHHHHHH HHHHHH      HH

      VI                      VII
251 LECADDRADL AKYICENODS ISSKLKECCE KPLLEKSHCI AEVENDEMPA
      HHHHHHHHHHH HHHHH      HHHHH      HHHHHHH H

301 DLPSLAADFV ESKDVCKNYA EAKDVFLGMF LYEYARRHPD YSVVLLLLRLA
      HHHH      HHHHHH      HHHHHHH HHHHHH      HHHHHHHH

      VIII
351 KTYETTLEKC CAAADPHECY AKVFDEFKPL VEEPQNLIKQ NCELFEQLGE
      HHHHHHHHHHH      HH      H      HHHHH HHHHHHHHHHH HHHHHHH

      IX
401 YKFQNALLVP YTKKVPQVST PTLVEVSRNL GKVGSKCCKH PEAKRMPCAE
      HHHHHHHHHHH HHHH      H HHHHHHHHHHH      HHH      HHHHHHHHH

      X                      XI
451 DYLSVVLNQL CVLHEKTPVS DRVTKCCTES LVNRRPPCFSA LEVDETYVPK
      HHHHHHHHHHH HHHHH      HHHHHHHHH      HHHHHHHH

501 EFNAETFTFH ADICTLSEKE RQIKKQTALV ELVKHKPKAT KEQLKAVMDD
      HHH      HHH HHHHMMHHHH HHH      HHHHHHHHH

      XII
551 FAAFVEKCCK ADDKETCFAE EGKKLVAAASQ AALGL
      HHHHHHHHH      HHHH HHHHHHHHHHH HH
  
```

Loop

I Val54-Asn61
 II Thr76-Asp89
 III Ala92-Glu100
 IV Gln170-Ala176
 V His247-Glu252
 VI Glu266-Glu277

Loop

VII Glu280-His288
 VIII Ala362-Glu368
 IX Lys439-Pro447
 X Val462-Lys475
 XI Thr478-Pro486
 XII Lys560-Thr566

Figure 10

a. Randomisation of Loop IV.

151 APELLFFAKR YKAAFTECCQ ^{IV}AADKAACLLP KLDEL RDEGK ASSAKQRLKC
 HHHHHHHHHH HHHHHHHHHH HHHHH HHHHHHHHHHH HHHHHHHHHHH

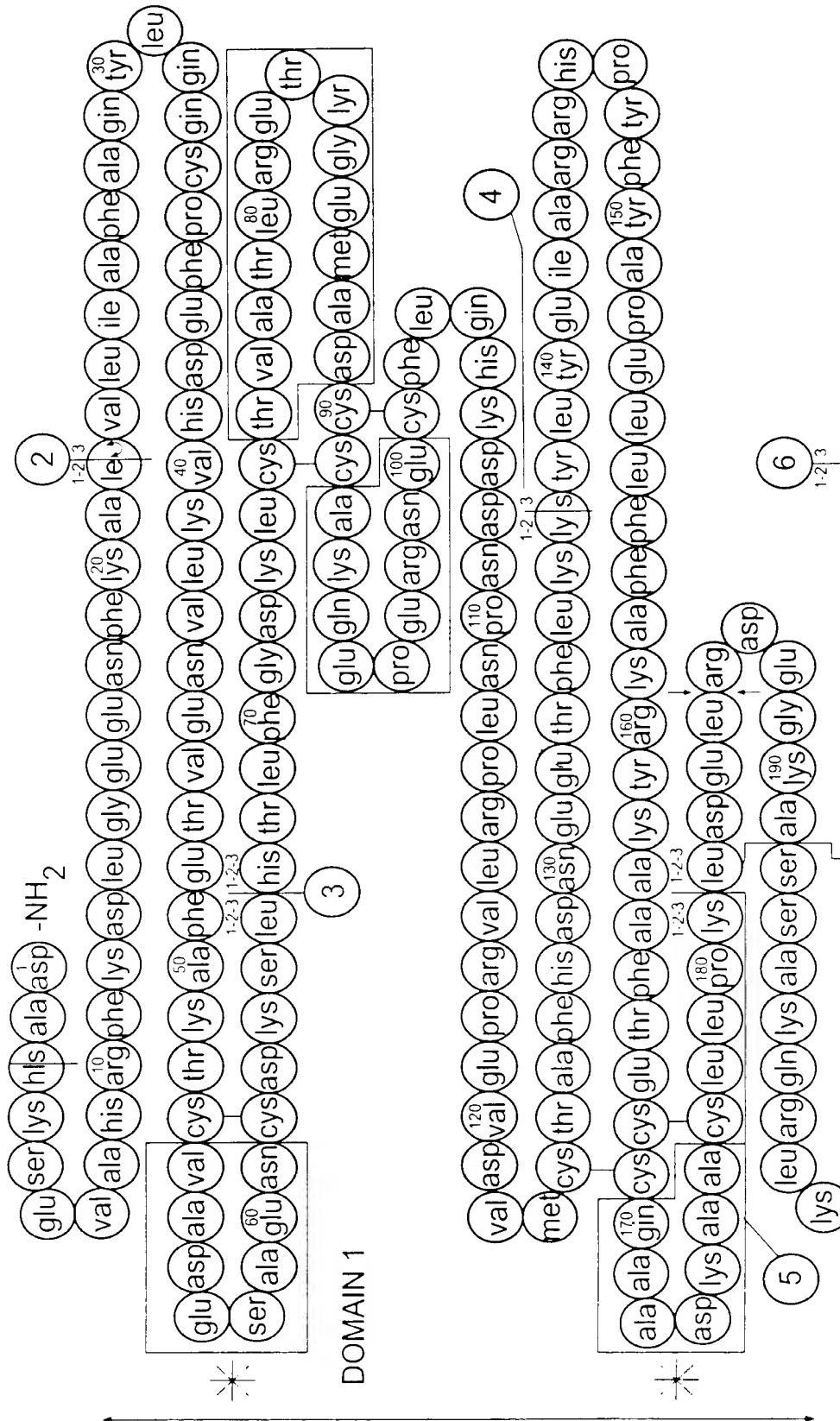
151 APELLFFAKR YKAAFTECCX ^{IV}XXXXXXCLLP KLDEL RDEGK ASSAKQRLKC
 HHHHHHHHHH HHHHHHHHHH HHHHH HHHHHHHHHHH HHHHHHHHHHH

X represents the mutation of the natural amino acid to any other amino acid. One, more or all of the amino acids can be changed in this manner. This figure indicates all the residues have been changed.

b. Insertion (or replacement) of Randomised sequence into Loop IV.

(X)_n
↓
^{IV}
151 APELLFFAKR YKAAFTECCQ AADKAACLLP KLDEL RDEGK ASSAKQRLKC
 HHHHHHHHHH HHHHHHHHHH HHHHH HHHHHHHHHHH HHHHHHHHHHH

The insertion can be at any point on the loop and a length where n would typically be 6, 8, 12, 20 or 25.



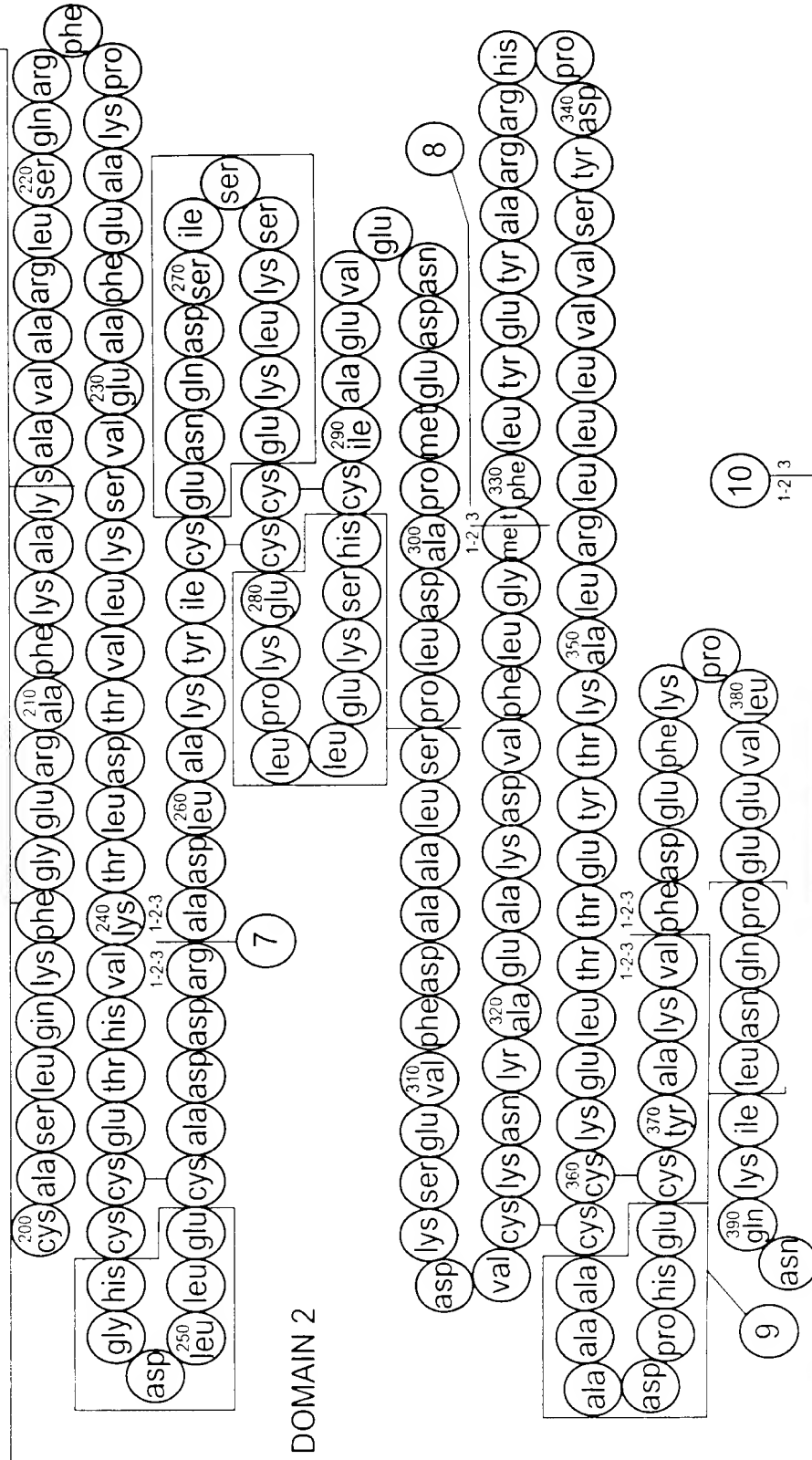
TO FIG. 11B

TO FIG. 11B

FIG. 11A

FROM FIG. 11A

FROM FIG. 11A



TO FIG. 11C

TO FIG. 11C

FIG. 11B

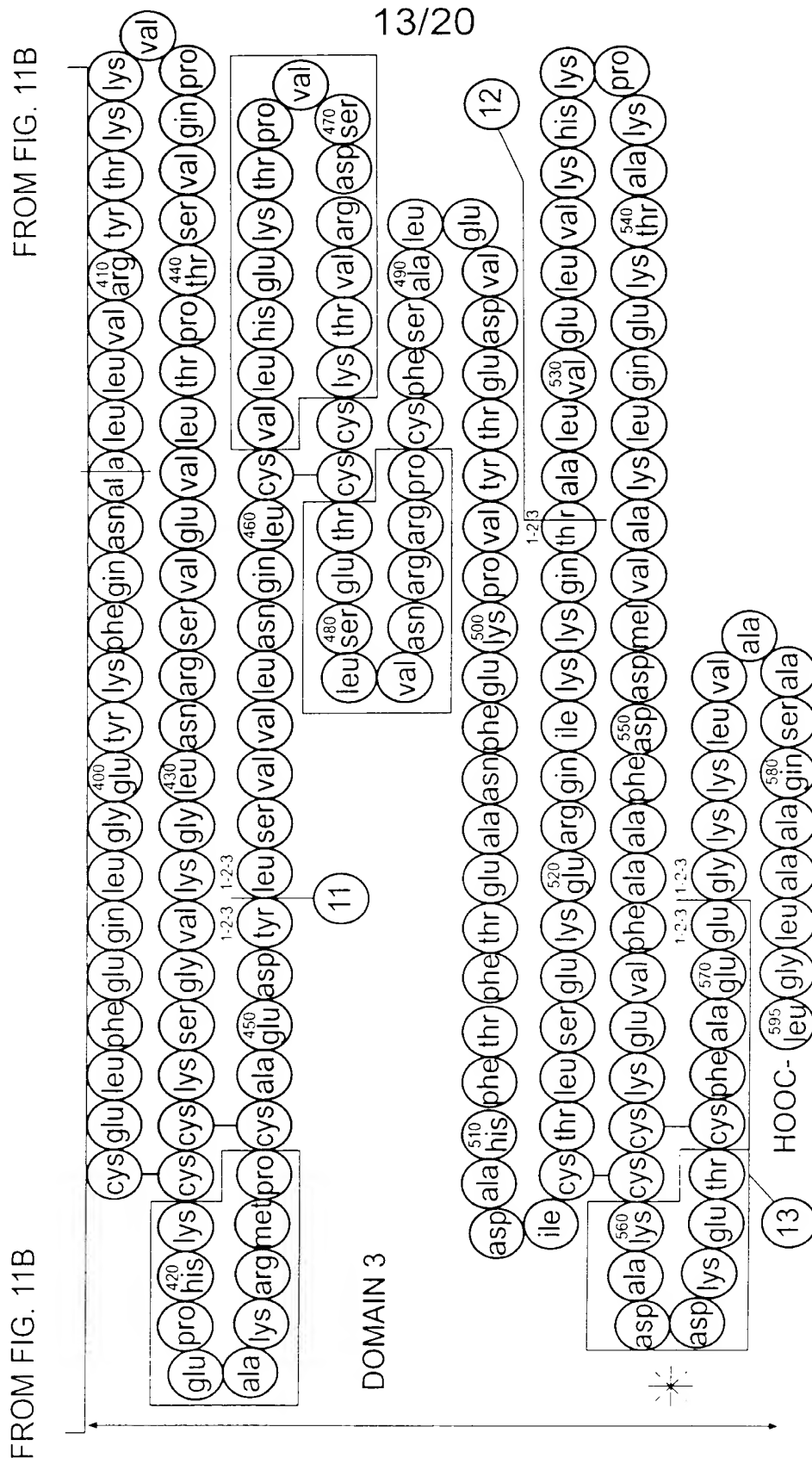


FIG. 11C



FIG. 12:
LOOP IV GLU170-A176

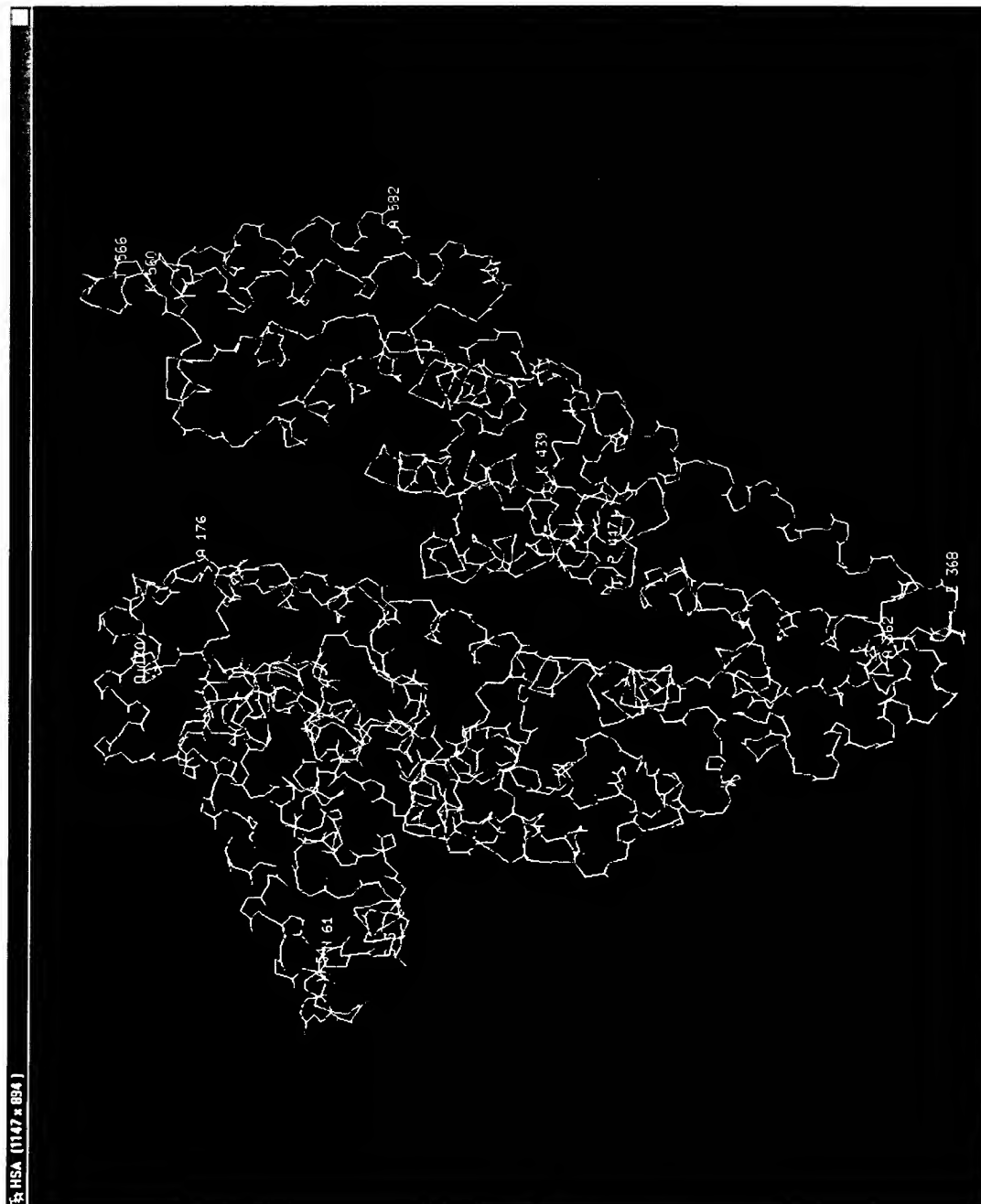


FIG. 13
TERTIARY STRUCTURE OF HA

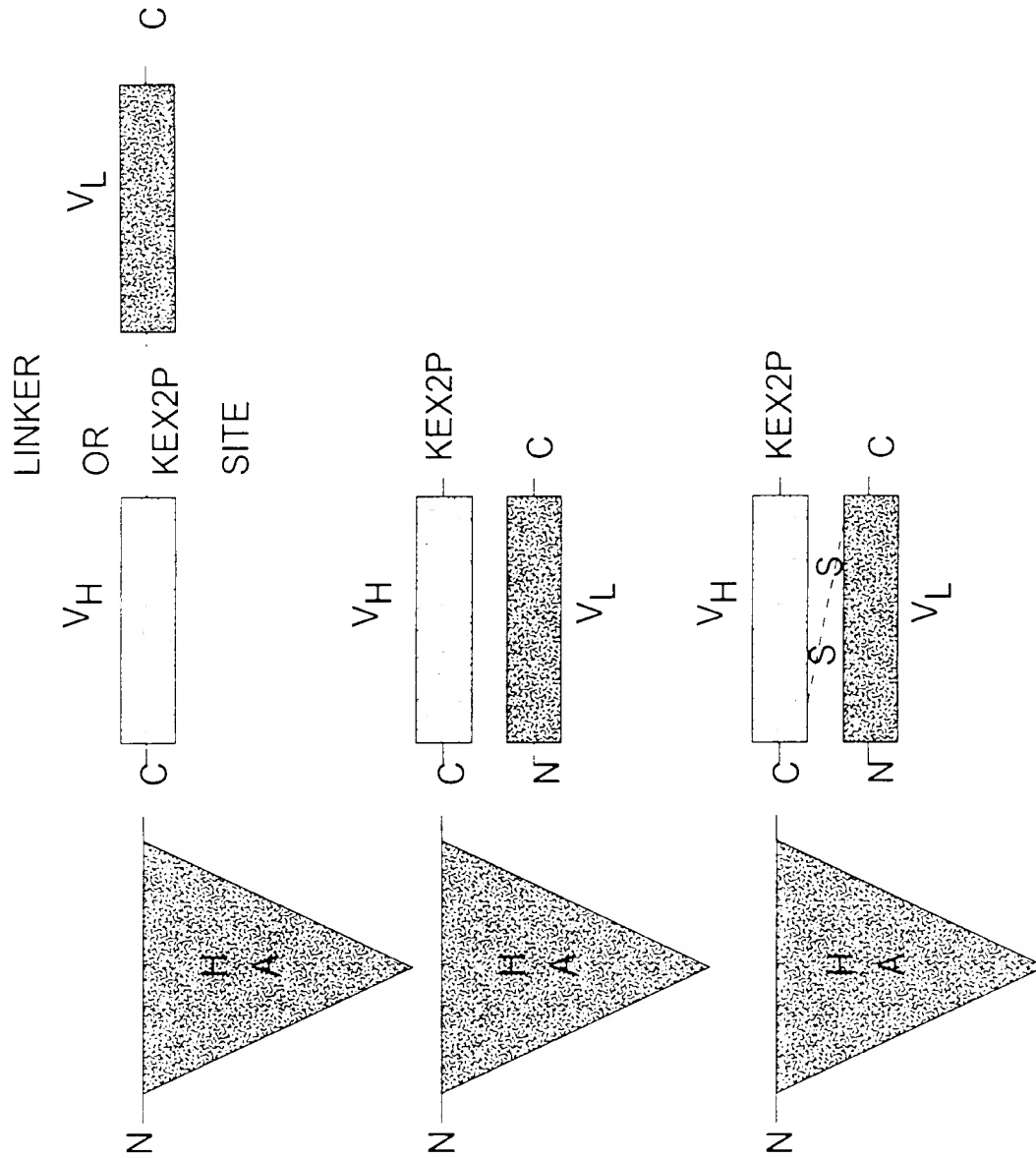


FIG. 14

1 GAT GCA CAC AAG AGT GAG GTT GGT CAT CCG TTT AAA GAT TTG GGA GAA GAA AAT TTC AAA 60
 1 D A H K S E V A H R F K D L G E E N F K 20

61 GGC TTG GTG ATT GGC TTT GGT CAG TAT CTT CAG CAG TGT CCA TTT GAA GAT CAT GTA 120
 21 A L V L I A F A Q Y L Q Q C P F E D H V 40

121 AAA TTA GTG AAT GAA GTA ACT GAA TTT GGA AAA ACA TGT GTT GGT GAT GAG TCA GCT GAA 180
 41 K L V N E V T E F A K T C V A D E S A E 60

181 AAT TGT GAC AAA TCA CTT CAT ACT CTT TTT GGA GAC AAA TTA TGC ACA GTT GCA ACT CTT 240
 61 N C D K S L H T L F G D K L C T V A T L 80

241 CGT GAA ACC TAT GGT GAA ATG GGT GAC TGC TGT GCA AAA CAA GAA CCT GAG AGA AAT GAA 300
 81 R E T Y G E M A D C C A K Q E P E R N E 100

301 TGC TTC TTG CAA CAC AAA GAT GAC AAC CCA AAA CTC CCG TTT GGT GAG CCA GAG GTT 360
 101 C F L Q H K D D N P N L P R L V R P E V 120

361 GAT GCG ATG TGC ACT GGT TTT CAT GAC AAT GAA GAG ACA TTT TTG AAA AAA TAC TTA TAT 420
 121 D V M C T A F H D H E E T F L K K Y L Y 140

421 GAA ATT GGC ACA AGA CAT CTT TAC TTT TAT GGC CCG GAA CTC CTT TTC TTT GCT AAA AGG 480
 141 E I A R R H P Y F Y A P E L L L F F A K R 160

Figure 15A

481 TAT AAA GCT GCT TTT ACA GAA TGT TGC CAA GCT GCT GAT AAA GCT GCC TGC CTG TTG CCA 540
 161 Y K A A F T E C C Q A A D K A A C L L P 180

541 AAG CTC GAT GAA CTT CCG GAT GAA GGG AAG GCT TCG TCT GGC AAA CAG AGA CTC AAA TGT 600
 181 K L D E L R D E G K A S S A K Q R L K C 200

601 GCC AGT CTC CAA AAA TTT GGA GAA AGA GCT TTC AAA GCA TGG GCA GTG GCT CGC CTG AGC 660
 201 A S L Q K K F G E R A F K A W A V A R L S 220

661 CAG AGA TTT CCC AAA GGT GAG TTT GCA GAA GTT TCC AAG TTA GTG ACA GAT CTT ACC AAA 720
 221 Q R F P K A E F A E V S K L V T D L T K 240

721 GTC CAC ACG GAA TGC TGC CAT GGA GAT CTG CTT GAA TGT GAT GAC AGG GCG GAC CTT 780
 241 V H T E C C H G D L L E C A D D R A D L 260

781 GCC AAG TAT ATC TGT GAA AAT CAG GAT TCG ATC TCC AGT AAA CTG AAG GAA TGC TGT GAA 840
 261 A K Y I C E N Q D S I S S K L K E C C E 280

841 AAA CCT CTG TTG GAA AAA TCC CAC TGC AAT GGC GAA GTG GAA AAT GAT GAG ATG CCT GCT 900
 281 K P L L E K S H C I A E V E N D E M P A 300

901 GAC TTG CCT TCA TTA GCT GCT GAT TTT GTT GAA AGT AAG GAT GTT TGC AAA AAC TAT GCT 960
 301 D L P S L A A D F V E S K D V C K N Y A 320

Figure 15B

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961 GAG GCA AAG GAT GTC TTC CTG GGC ATG TTT TTG TAT GAA TAT GCA AGA AGG CAT CCT GAT 1020
321 E A K D V F L G M F L Y E Y A R R H P D 340

1021 TAC TCT GTC GTG CTG CTG AGA CTT GCC AAG ACA TAT GAA ACC ACT CTA GAG AAG TGC 1080
341 Y S V V L L L R L A K T Y E T L E K C 360

1081 TGT GGC GCT GCA GAT CCT CAT GAA TGC TAT GCC AAA GTG TTC GAT GAA TTT AAA CCT CTT 1140
361 C A A A D P H E C Y A K V F D E F K P L 380

1141 GTG GAA GAG CCT CAG AAT TTA ATC AAA CAA AAC TGT GAG CTT TTT GAG CAG CTT GGA GAG 1200
381 V E E P Q N L I K Q N C E L F E Q L G E 400

1201 TAC AAA TTC CAG AAT GCG CTA TTA GTT CTT TAC ACC AAG AAA GTA CCC CAA GTG TCA ACT 1260
401 Y K F Q H A L L L V R Y T K K V P Q V S T 420

1261 CCA ACT CTT GTA GAG GTC TCA AGA AAC CTA GGA AAA GTG GGC AGC AAA TGT TGT AAA CAT 1320
421 P T L V E V S R N L G K V G S K C C K H 440

1321 CCT GAA GCA AAA AGA ATG CCC TGT GCA GAA GAC TAT CTA TCC GTG GTC CTG AAC CAG TTA 1380
441 P E A K R M P C A E D Y L S V V L N Q L 460

1381 TGT GTG TTG CAT GAG AAA ACG CCA GTA AGT GAC AGA GTC ACA AAA TGC TGC ACA GAG TCC 1440
461 C V L H E K T P V S D R V T K C C T E S 480

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Figure 15C

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1441 TTG GTG AAC AGG CGA CCA TGC TTT TCA GGT CTG GAA GPC GAT GAA ACA TAG GTT CCC AAA 1500
481 L V N R R P C F S A L E V D E T Y V P K 500

1501 GAG TTT AAT GCT GAA ACA TTC ACC TTC CAT GCA GAT ATA TGC ACA CTT TCT GAG AAG GAG 1560
501 E F N A E T F T F H A D I C T L S E K E 520

1561 AGA CAA ATC AAG AAA CAA ACT GCA CTT GTT GAG CTT GTG AAA CAC AAG CCC AAG GCA ACA 1620
521 R Q I K K Q T A L V E L V K H K P K A T 540

1621 AAA GAG CAA CTG AAA GCT GTT ATG GAT GAT TTC GCA GCT TTT GTA GAG AAG TGC TGC AAG 1680
541 K E Q L K A V M D D F A A F V E K C C K 560

1681 GCT GAC GAT AAG GAG AUC TGC TTT GGC GAG GAG GGT AAA AAA CTT GTT GCT GCA AGT CAA 1740
561 A D D K E T C F A E E G K K L V A A S Q 580

1741 GCT GGC TTA GGC TTA TAA CAT CTA CAT TTA AAA GCA TCT CAG 1782
581 A A L G L 585

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Figure 15D